What the Brainstem Stops Sending

Brainstem and basal forebrain neurons in early Alzheimer's disease: which functions fade with age, and what each one withdraws from the forebrain

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November 2026

The first of the short papers on the model's three stacked phases. Phase I begins in a handful of small nuclei that each send one chemical messenger to the whole forebrain. This paper takes them one at a time: what each supplies, what fades as a person ages towards the disease, and which corpus paper makes the case.

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Abstract

The first phase of the disease, in the model this site has built from the published record, begins in a handful of small nuclei at the base of the brain. Each of them makes one chemical messenger and sends it almost everywhere: noradrenaline from the locus coeruleus, serotonin from the raphe, acetylcholine from the nucleus basalis, dopamine from the ventral tegmental area. None of them carries information in the ordinary sense. They set the conditions under which the rest of the brain works: how awake it is, how well it sleeps, what it attends to, which memories it keeps, how much effort a goal is worth, and how fast it disposes of its own waste.

This paper is the first of a short series that explains the model one phase at a time. It asks two plain questions of each population. What does it supply? And what about that supply fades as a person ages towards the disease? The answers are drawn from the corpus's longer papers on each nucleus, and the primary studies those papers rest on.

Three findings organise the account. First, these neurons fail early and fail in function long before they die. Abnormal tau is already present in the locus coeruleus in the second and third decades of life, yet its neurons are not lost in number until the disease is half over; the axons go first, and the cell bodies decades later. Second, the supplies they withdraw are not only cognitive. Two of them are brakes on amyloid itself: serotonin tonically suppresses its production, and somatostatin, made by a forebrain interneuron that depends on cholinergic drive, licenses its disposal through the enzyme neprilysin. Two more, noradrenaline and acetylcholine, hold the brain's immune cells at rest. Third, the losses are selective in a way that teaches something. A cholinergic nucleus in the brainstem, the pedunculopontine, accumulates tangles and keeps its neurons, because it does not depend on a growth factor that the disease cuts off; what dies is not the cholinergic cell but the dependent one.

The model now draws its three phases as stacked steps rather than a sequence of hand-overs. This paper describes the base of that stack. It is a step that does not end when the next begins: the brainstem keeps failing underneath everything that follows. The paper closes with a summary table, a graded ledger of its claims, and the results that would undo them.

How to read this paper

This is a short paper by design. Each section below summarises a longer volume in the corpus, and each of those volumes carries its own full argument, evidence and ledger. Where this paper states a number it gives the primary source; where it states an interpretation it names the corpus paper that makes it, so the reader can go and check.

Claims are graded where they are made, using the four grades the corpus uses throughout. **Established** means replicated in human material by more than one group. **Probable** means good evidence with a gap, such as a single cohort or an animal result not yet confirmed in people. **Inference** means a conclusion drawn here, or in the corpus, from evidence gathered for another purpose. **Speculative** means coherent and untested.

One term needs fixing at the start. The model measures function by **connections**, not by cells. A neuron that has lost its connections but is still alive is silenced rather than dead, and the difference matters, because a silenced neuron may in principle be recovered. Synapse loss is the structural change that tracks cognitive decline most closely, which is why it is the unit used across the corpus.

1. The Base of the Stack

For most of its history the disease has been described by what accumulates in the cortex: plaques of amyloid between cells, tangles of tau inside them. The model this site has assembled describes it instead by what is lost, where and when. Read that way, the published record settles into an order. Connections are lost first in a few small nuclei of the brainstem and basal forebrain, then in the hippocampus, then in the cortex. The corpus calls these three stretches Phase I, Phase II and Phase III.

The phases were first drawn as a relay, each handing over to the next. They are now drawn as stacked steps. Phase I begins in the third decade of life. Phase II begins in the sixth, on top of it. Phase III begins in the eighth, on top of both. No step ends when the next begins. A person of seventy-five is

carrying all three, and the brainstem is still failing underneath the hippocampus and the cortex. The steps are joined by two specified transitions, which the corpus calls bridges: the first is the withdrawal of noradrenaline from the brain's immune cells, the second the digestion of the protective net around inhibitory neurons.

This paper is about the bottom step. It covers five populations of neurons and one forebrain neighbour:

- the **locus coeruleus**, which makes noradrenaline;
- the **raphe nuclei**, which make serotonin;
- the **nucleus basalis of Meynert**, which makes acetylcholine for the cortex;
- the **ventral tegmental area**, which makes dopamine for memory and motivation;
- the **pedunculopontine nucleus**, a brainstem cholinergic group that turns out to be the control case;
- and the **somatostatin interneuron**, a forebrain cell that is not part of the brainstem but is among the first casualties of what the brainstem stops sending.

The nucleus basalis sits in the basal forebrain rather than the brainstem proper. It is included because the model groups it with the brainstem nuclei: it shares their architecture, their early failure and their kind of job.

2. What the Population Shares

The neurons of the first step look alike in four ways, and the likeness is the beginning of an explanation for why they go first.

An enormous axon. Each of these neurons sends a thin, branching, mostly unmyelinated axon across very large territories. A single coerulean neuron accompanies some twenty metres of cerebral capillary (Matchett and colleagues, 2021); a dorsal raphe neuron's reconstructed axon in the rat runs to nearly nineteen centimetres (*The Unpicked Seam*). Maintaining a structure of that size costs energy continuously, and supplying its far end depends on

transport along the whole of its length.

A pacemaker that does not rest. These neurons fire on their own, tonically, through the waking day. The firing imposes a continuous load of calcium and a continuous demand for energy. The locus coeruleus fires at about two spikes per second in waking, below one in slow-wave sleep, and almost not at all in REM sleep (Aston-Jones and Bloom, 1981), so sleep is the only time the load is lifted.

No protective net. Many neurons elsewhere in the brain are wrapped in a lattice of extracellular matrix, the perineuronal net. In subcortical regions of the Alzheimer brain, neurons that carry such a net are protected against tau pathology (Morawski and colleagues, 2010). The coerulean and raphe neurons are constitutionally without one.

A single, broadcast job. Each population supplies one modulator to the whole forebrain. Its loss produces no paralysis, no focal sign and no single symptom that sends a patient to a neurologist. It produces changes that are easily mistaken for ordinary ageing: worse sleep, less drive, poorer attention, a little more forgetting.

Two of these four properties are about energy and one is about protection. That is why the corpus calls Phase I *Bioenergetic Ignition*: the first failure is a failure to sustain an expensive structure, and it is metabolic before it is anything else (*The Shape of the Disease*). The grade on that interpretation is **inference**. The neuropathology it explains is **established**.

3. The Locus Coeruleus: Noradrenaline

What it supplies

The locus coeruleus is a nucleus of a few tens of thousands of neurons on each side of the pons, no larger than a grain of rice. It is the brain's main source of noradrenaline, and it supplies it to the entire cortex, the hippocampus, the thalamus and the cerebellum. Four of its supplies matter here.

- **Waking and attention.** Noradrenaline sets the depth of wakefulness and the gain of attention. The nucleus's firing anticipates shifts in the

sleep–wake cycle (Aston-Jones and Bloom, 1981).

- **The architecture of sleep.** The nucleus has to oscillate in one sleep state and fall silent in another. During non-REM sleep, slow infra-slow oscillations of noradrenaline drive the vasomotion that pumps the brain's glymphatic clearance; abolishing them abolishes the clearance (Hauglund and colleagues, 2025). During REM sleep it falls silent.
- **A brake on the brain's immune cells.** Noradrenaline holds microglia in their resting state. When the locus coeruleus is lesioned in amyloid-bearing mice, microglia lose their ability to clear amyloid and inflammation rises (Heneka and colleagues, 2010).
- **The consolidation of memory.** Coerulean axons release dopamine as well as noradrenaline in the hippocampus, and that release helps decide which everyday memories persist (Takeuchi and colleagues, 2016).

What fades, and when

The locus coeruleus is the first place in the human brain to accumulate abnormal tau. Pretangle material is demonstrable there from the second and third decades of life (Braak and Del Tredici, 2011), across a survey of 2,332 brains spanning ages one to one hundred (Braak and colleagues, 2011). In brains with no cortical tangles at all, 7.9 per cent of coerulean neurons already carry hyperphosphorylated tau inclusions (Ehrenberg and colleagues, 2017). **Established.**

The neurons themselves are not lost for a long time. Stereological counts across the whole staging series find neuronal number preserved through Braak stages 0 to II and falling only from stage III (Theofilas and colleagues, 2017). The interval between the appearance of tau and the death of the neuron has been put at about a quarter of a century (Matchett and colleagues, 2021). By amnestic mild cognitive impairment about thirty per cent of the neurons are gone, with a further quarter lost by mild-to-moderate dementia (Kelly and colleagues, 2017), and the end-stage loss is the largest of any subcortical nucleus (Zarow and colleagues, 2003). **Established.**

What fails in the interval is the axon. In an amyloid knock-in mouse, noradrenergic fibres in a coerulean target field are 14 per cent lost at two months, 27 per cent at three and 33 per cent at six, while the number of coerulean cell bodies is indistinguishable from normal at twelve months. In human tissue the matching fibre degeneration is already present at Braak

stages 1 to 2 (Meyer and colleagues, 2025). The axon is not lost because the cell died. It is removed while the cell is alive: microglia in the target field recognise the coerulean axons and engulf them, and reducing that engulfment genetically preserves both the axons and the function they serve (Meyer and colleagues, 2025). *The Coerulean Clock* argues that what marks the axon for removal is the neuron's own overactive firing, calls this the axon clock, and holds that it, not the death of the cell body, is the clinically relevant one. **Probable**: the mouse result is strong and the human fibre data agree; the firing mechanism is the corpus's **inference**.

The corpus offers a chemical reason why this nucleus tangles first. The locus coeruleus expresses monoamine oxidase A, and the oxidation of its own transmitter by that enzyme produces a reactive aldehyde, DOPEGAL. DOPEGAL activates an enzyme, asparaginyl endopeptidase, that cuts tau into a fragment prone to aggregate (Kang and colleagues, 2020; Zhang and colleagues, 2014). APOE4, the strongest genetic risk factor for the disease, inhibits the transporter that packages noradrenaline into vesicles and so leaves more of it in the cytoplasm to be oxidised (Kang and colleagues, 2021). *The First Ember* sets out the chain. **Probable** in its parts, measured in model systems; the joined chain is **inference**.

What the loss costs

The first clinical sign of a failing locus coeruleus is not forgetting. It is broken sleep. In cognitively unimpaired older adults, worse structural integrity of the nucleus already tracks more frequent awakenings at night (Van Egroo and colleagues, 2021). The model is careful about direction: it does not argue that poor sleep causes the disease. The coerulean tau comes first, and disturbed sleep is among the earliest things it produces. But once present, disturbed sleep becomes a lever on what follows, because the nucleus is also the pump for night-time clearance.

The loss of the brake on microglia is the first bridge of the model, the point at which Phase I sets off Phase II. The same ascending axons that withdraw noradrenaline from the hippocampus are the route by which, on the model's reading, tau is carried there. That joint is graded **inference** throughout the corpus and is the part it most wants other laboratories to test (*The Coerulean Interface*; *The Shape of the Disease*).

4. The Raphe Nuclei: Serotonin

What it supplies

The raphe nuclei lie along the midline seam of the brainstem and contain nearly all of the brain's serotonin. The rostral group, and the dorsal raphe nucleus above all, supplies the forebrain. *The Unpicked Seam* lists seven things that supply does; three matter most here.

- **A brake on amyloid production.** This is the least expected and the most consequential. Serotonin signalling lowers the level of amyloid-β between cells in mice, and people exposed to selective serotonin reuptake inhibitors carry less amyloid on imaging (Cirrito and colleagues, 2011). In healthy volunteers, a single course of citalopram slowed the production of amyloid-β in cerebrospinal fluid by 37 per cent (Sheline and colleagues, 2014). The route runs through the 5-HT4 receptor, which binds and traffics ADAM10, the enzyme that cuts the amyloid precursor protein in the harmless direction (Cochet and colleagues, 2013).
- **Sleep and the night.** Serotonin consolidates sleep, and it is the chemical substrate for melatonin.
- **Mood, but less than assumed.** The serotonergic loss in Alzheimer's disease is not the cause of its depression. Comparing four groups at post-mortem, Alzheimer brains were markedly depleted of dorsal raphe serotonergic neurons, brains from primary late-life depression were not, and Alzheimer patients with and without depression did not differ (Hendricksen and colleagues, 2004).

What fades, and when

The raphe fails early, after the locus coeruleus and before the cortex. Braak's survey places abnormal tau in the serotonergic raphe at pretangle stage c, before any cortical involvement (Braak and colleagues, 2011), and the dorsal raphe shows phospho-tau change before the transentorhinal region does (Grinberg and colleagues, 2009). At Braak stage 0, 2.6 per cent of dorsal raphe neurons already carry tau inclusions (Ehrenberg and colleagues, 2017). **Established.**

It fails severely. A meta-analysis of sixty-seven studies ranks raphe neuron loss at an effect size of 1.79 standard deviations, behind the nucleus basalis and the locus coeruleus but well ahead of the substantia nigra (Lyness and colleagues, 2003); direct counts put the loss near forty per cent of the nucleus (Aletrino and colleagues, 1992). **Established.**

The raphe teaches something by what it lacks. It does not carry the coeruleus's chemical liability: its neurons express monoamine oxidase B rather than A, so they do not make DOPEGAL in the same way. Yet they tangle nearly as early. *The Unpicked Seam* draws the conclusion that the shared cause of early failure is architectural rather than chemical: the long arbor, the pacemaker and the missing net. **Inference**, and a useful one, because it says where to look.

What the loss costs

A nucleus that begins to fail in the third decade is withdrawing a tonic brake on amyloid production across the whole cortex, decades before the first plaque is counted (*The Unpicked Seam*; *The Fifty-Year Prescription*). That is a Phase I event with a Phase III consequence, and it is the clearest example in this paper of how the bottom step feeds the top one.

The trial record is close to uniformly negative, and the corpus reports it in full. The 5-HT6 antagonist idalopirdine failed three trials enrolling 2,525 patients (Atri and colleagues, 2018). Citalopram reduced agitation in Alzheimer's disease while worsening cognition and prolonging the cardiac QT interval (Porsteinsson and colleagues, 2014). The corpus's reading is that the target was right and the timing was wrong: the evidence describes a lesion that matters in midlife, and every trial enrolled people decades later. That reading is **inference**, and it is testable.

5. The Nucleus Basalis: Acetylcholine

What it supplies

The nucleus basalis of Meynert supplies acetylcholine to the cortex. Its loss gave the field its first mechanism and its first drug class (Whitehouse and colleagues, 1981, 1982). *The Gate and the Ransom* argues that the field misread what the nucleus does, and what it loses first.

- **Attention, not storage.** Acetylcholine in the cortex rises in sub-second bursts when a cue is detected, and the timing of those bursts predicts whether the cue is noticed (Parikh and colleagues, 2007). The nucleus is a gate on attention and plasticity rather than a memory store.
- **The difference between sleep states.** Cholinergic neurons fire with the theta rhythm in waking and REM sleep and almost stop in slow-wave sleep. That silence is needed: raising acetylcholine during slow-wave sleep in healthy people abolishes the consolidation of declarative memory (Gais and Born, 2004). The signal is a contrast, not a level.
- **A brake on inflammation.** Loss of basal forebrain volume in cognitively normal adults with abnormal amyloid and tau tracks rising markers of microglial activation, TREM2 and complement C3 (Schmitz and colleagues, 2020). Like the locus coeruleus, the nucleus may hold the brain's immune cells at rest. **Probable.**

What fades, and when

The nucleus does not die first. It lets go of its growth factor first. Counting neurons that display TrkA, the receptor for nerve growth factor, Mufson and colleagues found about 197,000 in the cognitively normal, 106,000 in mild cognitive impairment and 87,000 in Alzheimer's disease: a loss of nearly half, complete before dementia (Mufson and colleagues, 2000). Counting the same nucleus for the enzyme that makes acetylcholine found about 210,000 cholinergic neurons per hemisphere in the normal elderly and no significant loss in mild cognitive impairment or early disease (Gilmor and colleagues, 1999). Cortical choline acetyltransferase activity is unchanged or even raised in mild cognitive impairment (DeKosky and colleagues, 2002). Read together, with the caution that they are different series, the numbers describe a cell that is still there and still cholinergic, and has stopped displaying the receptor it cannot live without. **Probable.**

The reason is that the nucleus holds its survival on loan. It depends on nerve growth factor supplied by the cortex it projects to, and that factor is

released as a precursor that must be matured outside the cell by a protease cascade and is degraded by MMP-9 (Bruno and Cuello, 2006). In mild cognitive impairment the precursor rises (Peng and colleagues, 2004), MMP-9 activity rises (Bruno and colleagues, 2009), and TrkA falls while the co-receptor p75 is unchanged (Counts and colleagues, 2004). Nerve growth factor protein is increased throughout the Alzheimer brain while falling in the nucleus basalis itself (Scott and colleagues, 1995). *The Gate and the Ransom* reads this as a failure of delivery: the factor is made, but not matured and not received. **Probable** for each measurement; the reading is **inference**.

In living people, basal forebrain volume falls early and predicts later degeneration of the entorhinal cortex, not the other way round (Schmitz and Spreng, 2016; Fernández-Cabello and colleagues, 2020). **Probable.**

What the loss costs

The cost is attention, the depth of the difference between sleep states, and a brake on inflammation. The therapeutic lesson is sharp. The disease flattens a rhythm; a cholinesterase inhibitor raises an average. The drugs work, and the effect is small (Birks, 2006), which the corpus argues is the predictable result of treating a loss of contrast with a steady supply. **Inference.**

There is a second cost, carried by a different cell, and it is taken up in Section 8.

One further point about this cell belongs to the fourth paper in this series rather than to this one. Because its axon is so long, the growth factor it depends on is picked up at the far end and carried home on a sorting compartment called an endosome, so a fault in that compartment cuts the line between the terminal and the nucleus; *The Long Way Back* sets out the evidence that this is where the lesion sits.

6. The Ventral Tegmental Area: Dopamine

What it supplies

The ventral tegmental area, in the floor of the midbrain, is the source of the brain's mesolimbic and mesocortical dopamine. *The Price and the Permission* names its two jobs in its title.

- **The price.** Dopamine sets how much effort a goal is worth. Its withdrawal is the best-characterised chemistry of lost motivation.
- **The permission.** Dopamine does not carry the content of a memory, but it decides whether the memory is kept. A dopaminergic signal in the hippocampus, arriving in the hours around an event, converts a decaying trace into a lasting one (Takeuchi and colleagues, 2016).

What fades, and when

In amyloid-bearing mice, the dopaminergic neurons of this nucleus begin dying at three months of age, before any plaque has formed, and the loss is confined to the mesolimbic neurons; the neighbouring substantia nigra, which fails first in Parkinson's disease, is untouched (Nobili and colleagues, 2017). Every classical theory of dopaminergic vulnerability predicts the opposite ranking, which is itself informative. **Probable**, in models.

The human evidence is thinner, and the corpus says so precisely. The nucleus was tied to dementia in a 1988 case series of six brains (Torack and Morris, 1988). Midbrain volume and connectivity are reduced in people with mild cognitive impairment and track the cognitive signature of the disease (De Marco and Venneri, 2018). But there is no published unbiased count of dopaminergic neurons in the human ventral tegmental area in Alzheimer's disease. The nucleus has an experimental literature, an imaging literature, and no autopsy census. **Inference** for the human claim.

What the loss costs

The clinical signature is apathy. In cognitively normal people apathy carries roughly three times the odds of progressing to mild cognitive impairment and twice the odds of progressing to dementia, and in mild cognitive impairment it shortens the time to conversion (*The Price and the Permission*, which reviews the meta-analyses). Apathy is the second of the three early complaints most often written off as ageing. Methylphenidate improves it in patients (Mintzer and colleagues, 2021), which fits a dopaminergic lesion without proving one. **Established** for the prognostic association; **inference** for the attribution to this nucleus.

7. The Pedunculopontine Nucleus: The Cell That Survives

Not every nucleus at the base of the stack dies, and the one that does not is as informative as the ones that do.

The pedunculopontine nucleus is a cholinergic group in the upper brainstem, a few millimetres from the locus coeruleus. With its neighbour, the laterodorsal tegmental nucleus, it supplies most of the acetylcholine that reaches the thalamus, and it is part of the circuitry of REM sleep. It has every risk factor the field attributes to the cells this disease destroys: it is cholinergic, large, diffusely projecting and metabolically expensive, and it accumulates Alzheimer tau. And it keeps its neurons. Woolf and colleagues found tangles but no loss of cell bodies (Woolf and colleagues, 1989); design-based stereology found neuron number indistinguishable from control (Eser and colleagues, 2018). The one dissenting study measured a reduction of large neurons only (Jellinger, 1988), which *The Standing Relay* reads as shrinkage rather than death. **Established.**

The reason is a molecular difference noticed in 1989 and not read against this disease until the corpus did so. Nucleus basalis neurons carry high levels of the nerve growth factor receptor; pedunculopontine neurons do not (Mesulam and colleagues, 1989). The pedunculopontine neuron is not dependent on the supply the disease cuts off. What the disease kills, on this

reading, is not the cholinergic cell but the dependent cell. **Inference**, from two established findings.

The nucleus does not die, but its function may still fade. Tau in the pedunculopontine nucleus tracks a lengthened delay to REM sleep and a smaller share of it, and in the Framingham cohort a smaller share of REM sleep predicted dementia (Pase and colleagues, 2017). Whether the channel from this nucleus to the thalamus still carries its traffic has never been measured (*The Standing Relay*).

8. The First Neighbour: Somatostatin and Neprilysin

The somatostatin interneuron is not a brainstem cell. It lives in the hippocampus and cortex, and the corpus files it with Phase II. It is included here because it is among the first cells to suffer from what the brainstem stops sending, and because its loss removes the second of the two amyloid brakes this paper has to describe.

What it supplies

The oldest finding in this disease that is not about acetylcholine is that somatostatin is depleted from the Alzheimer cortex (Davies, Katzman and Terry, 1980). The peptide does two things that matter here.

- **It licenses the disposal of amyloid.** Somatostatin raises the activity of neprilysin, the brain's main amyloid-β-degrading enzyme. Mice lacking somatostatin have altered hippocampal neprilysin and more of the aggregation-prone form of amyloid-β (Saito and colleagues, 2005). The pathway runs from the somatostatin receptor through α-endosulfine to ATP-sensitive potassium channels, and acting on those channels activates neprilysin, reduces amyloid deposition and rescues memory in mice (Watamura and colleagues, 2022). The SST1 and SST4 receptors carry the effect between them; deleting both reduces neprilysin, worsens amyloid pathology, and an agonist at both reverses it (Nilsson and colleagues, 2026). **Established** in animals, by loss and by gain of function.

- **It gates the input to memory.** The somatostatin interneurons of the hippocampus control how the entorhinal cortex's input reaches CA1 (Leão and colleagues, 2012). *The Homeward Vector* argues that this gate is what lets an internal map be reset by landmarks, and that losing it is why people with early disease get lost. That is **inference**.

What fades, and when

Somatostatin interneurons are lost early, in cognitively still-normal stages, in the largest single-cell atlas of the disease (Gabitto and colleagues, 2024). In an amyloid model, the interneurons that gate the CA1 input fail at both ends, and the mechanism identified was reduced cholinergic drive (Schmid and colleagues, 2016). That is the link to the bottom step: the acetylcholine the nucleus basalis stops sending is part of what keeps this cell working. **Probable.**

What the loss costs

The Unnetted Governor states the consequence as a loop. Somatostatin licenses the disposal of amyloid; amyloid injures the somatostatin cell; fewer somatostatin cells mean less disposal, and therefore more amyloid. The loop amplifies itself, and it starts early. The corpus adds a claim of address: the neprilysin that depends on somatostatin receptors is concentrated in the very layer of the hippocampus where the entorhinal input arrives and where the somatostatin cell's axon ends (Nilsson and colleagues, 2026). The two facts are measured; the joining is **inference**, and the volume names it as its most important untested claim.

Getting lost is the third of the early complaints. With broken sleep from the locus coeruleus and apathy from the ventral tegmental area, it completes the set the model predicts should come before forgetting.

9. What the Step Adds Up To

Table 1 gathers the populations in one place.

Table 1. The bottom step, population by population. Timing for each population is given in its section; dates are nominal and individuals differ.

Population	Messenger	What it supplies	What fades first	Corpus paper
Locus coeruleus	Noradrenaline	Waking, attention, night-time clearance, a brake on microglia	The axon, decades before the cell body	*The Coerulean Clock*
Raphe nuclei	Serotonin	A brake on amyloid production, sleep, melatonin substrate	Tau after the coeruleus, before cortex; ~40% loss	*The Unpicked Seam*
Nucleus basalis	Acetylcholine	Attention, the contrast between sleep states, a brake on inflammation	The growth-factor receptor, before the cell	*The Gate and the Ransom*
Ventral tegmental area	Dopamine	Effort and motivation; the permission to keep a memory	Mesolimbic neurons, in mice before plaques	*The Price and the Permission*
Pedunculopontine	Acetylcholine	Thalamic acetylcholine, REM sleep	Function, not number: tangles without loss	*The Standing Relay*
Somatostatin interneuron	Somatostatin	Licence for neprilysin to clear amyloid; the input gate to memory	Early loss; driven partly by lost cholinergic input	*The Unnetted Governor*

Read across, four things stand out.

Function goes before the cell. The coerulean axon is removed while its cell body lives. The nucleus basalis gives up its receptor before it gives up its transmitter, and its transmitter before it dies. The pedunculopontine nucleus tangles and never dies at all. In each case there is a long interval in which the neuron is silenced rather than lost. That interval is where the model locates its hope, because a silenced neuron may be recoverable and a dead one is not.

The step does not end. None of these populations recovers when Phase II begins. Their loss of connections keeps rising through the sixth, seventh and eighth decades. A therapy aimed at this step is therefore not only a therapy for the young: the step is still active in the old, even if the window for some treatments has closed.

The step loosens two brakes on amyloid and two on inflammation. Serotonin brakes amyloid production; somatostatin licenses its disposal. Noradrenaline and acetylcholine hold microglia at rest. All four supplies fall in the first step. That is how the bottom of the stack sets up the top: the amyloid that defines the disease's later decades, and the inflammation that defines its middle, are both made easier by what the brainstem has already stopped sending.

The first symptoms are not memory symptoms. Broken sleep, apathy and getting lost are the three complaints the model predicts first, and each maps to a population in this paper. They are the complaints most often written off as ordinary ageing.

10. Graded Ledger

Table 2. Each claim in this paper, with its grade and the sources it rests on.

#	Claim	Grade	Basis
1	Abnormal tau appears first in the locus coeruleus, from the 2nd–3rd decade	Established	Braak and Del Tredici 2011; Braak et al. 2011; Ehrenberg et al. 2017
2	Coerulean neuron number is preserved to Braak II and falls from III	Established	Theofilas et al. 2017; Kelly et al. 2017
3	Coerulean axons are lost while the cell body lives	Probable	Meyer et al. 2025 (mouse; human fibre data concordant)
4	The shared cause of early brainstem failure is architectural (arbor, pacemaker, no net)	Inference	*The Unpicked Seam*; Morawski et al. 2010; Matchett et al. 2021

#	Claim	Grade	Basis
5	DOPEGAL–AEP chemistry contributes to coerulean tau	Probable (parts); inference (chain)	Kang et al. 2020, 2021; Zhang et al. 2014
6	Noradrenaline holds microglia at rest; its loss is the first bridge	Probable (mouse); inference (bridge)	Heneka et al. 2010; *The Coerulean Interface*
7	Raphe loss is early, severe and not the cause of depression	Established	Lyness et al. 2003; Grinberg et al. 2009; Hendricksen et al. 2004
8	Serotonin tonically suppresses amyloid production	Probable	Cirrito et al. 2011; Sheline et al. 2014; Cochet et al. 2013
9	Nucleus basalis neurons lose TrkA before they lose their transmitter or die	Probable	Mufson et al. 2000; Gilmor et al. 1999; DeKosky et al. 2002
10	The nucleus basalis lesion is a failure of growth-factor delivery	Inference	Bruno and Cuello 2006; Peng et al. 2004; Scott et al. 1995
11	Ventral tegmental dopamine neurons are lost before plaques, sparing the nigra	Probable (mouse only)	Nobili et al. 2017
12	The pedunculopontine nucleus tangles without losing neurons	Established	Woolf et al. 1989; Eser et al. 2018
13	Growth-factor dependence, not cholinergic phenotype, marks the cells that die	Inference	Mesulam et al. 1989; *The Standing Relay*
14	Somatostatin licenses neprilysin-mediated amyloid disposal	Established (animal)	Saito et al. 2005; Watamura et al. 2022; Nilsson et al. 2026
15	Somatostatin interneuron failure is driven in part by lost cholinergic input	Probable	Schmid et al. 2016
16	The first step continues to worsen after the second begins	Inference	Site connection-loss curves; *The Shape of the Disease*

11. What Would Change This Account

The account above would need rewriting if any of the following were found.

- A human stereological count showing ventral tegmental dopamine neurons intact in Alzheimer's disease. The nucleus would then leave the first step.
- Evidence that coerulean axon loss in people follows, rather than precedes, the loss of the cell body. The axon clock would fail, and with it the case for treating the axon rather than the cell.
- A brainstem nucleus that is growth-factor dependent and survives, or one that is independent and dies. Either would break the reading offered for the pedunculopontine contrast.
- A properly timed trial, in midlife, of serotonergic or somatostatin-receptor treatment that changes neither amyloid production nor disposal. The amyloid brakes would then be smaller than claimed.
- Longitudinal evidence that brainstem connection loss stops or reverses once hippocampal involvement begins. The step model would revert to a relay.

The next paper in this series takes up the second step: the hippocampus, and the brain's immune cells as they lose their resting state.

Corpus papers drawn on

The Shape of the Disease (Phase overview). *The Coerulean Clock*: The Timing of Locus Coeruleus Loss in Alzheimer's Disease: Axon Before Soma. *The First Ember*: Tau Kindling in the Locus Coeruleus: Asparaginyl Endopeptidase, DOPEGAL and PP2A. *The Coerulean Interface*: The Brainstem Origin of Alzheimer's. *The Unpicked Seam*: The Raphe Nuclei in Alzheimer's Disease as a Subject in Their Own Right. *The Fifty-Year Prescription*. *The Gate and the Ransom*: The Cholinergic Nucleus Basalis in Alzheimer's Disease: Why the Receptor Is Surrendered. *The Price and the Permission*: The Ventral Tegmental Area in Alzheimer's Disease: Vulnerability, Trajectory, Disinhibition. *The*

Standing Relay: The Pedunculopontine Nucleus in Alzheimer's Disease: Tangle Burden Without Neuron Loss. *The Unnetted Governor*: The Somatostatin Interneuron in Alzheimer's Disease. *The Homeward Vector*: Wandering in Alzheimer's Disease. All are available in full at AdultCognitiveDisease.com.

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